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EXAMINER	
BRADLEY, CHRISTINA	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,062	DIOGUARDI, FRANCESCO SAVERIO	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-21 are cancelled. All rejections of these claims are now moot. Claims 32-53 are pending. Claim 32 was amended and claims 33-53 were newly added in the response filed 11/26/2008.

Withdrawn Claim Rejections - 35 USC § 112

2. The rejection of claim 32 under 35 U.S.C. 112, first paragraph, is withdrawn in light of the arguments filed 11/26/2008.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 32-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 32-53 are drawn to compositions comprising the amino acids leucine, isoleucine, valine, lysine, threonine, histidine, methionine, phenylalanine, tryptophan, tyrosine and cysteine, or pharmaceutically acceptable derivatives of each of the aforementioned amino acids. The instant specification does not define the term derivative. The online medical dictionary defines derivative as a chemical substance derived from another substance either directly or by modification or partial substitution. Thus, the scope of claims 32-53 encompasses compositions comprising any chemical substance derived from leucine, isoleucine, valine, lysine,

threonine, histidine, methionine, phenylalanine, tryptophan, tyrosine and cysteine directly, or any chemical substance consisting of leucine, isoleucine, valine, lysine, threonine, histidine, methionine, phenylalanine, tryptophan, tyrosine or cysteine that has been modified or partially substituted. The instant specification has reduced to practice only embodiments of the invention in which the composition comprises leucine, isoleucine, valine, lysine, threonine, histidine, methionine, phenylalanine, tryptophan, tyrosine and cysteine. There are no embodiments reduced to practice comprising derivatives of these amino acids. The instant specification discloses only one partial structure of an amino acid derivative, a pharmaceutically acceptable salt of the amino acids (paragraph 0070). The specification does not disclose any additional amino acid derivative nor does it describe the chemical or physical properties of amino acid derivatives or a correlation of the structure of amino acid derivatives and the function in the claimed methods. Based on this disclosure, the skilled artisan would recognize that Applicant was in possession of compositions comprising the amino acids leucine, isoleucine, valine, lysine, threonine, histidine, methionine, phenylalanine, tryptophan, tyrosine and cysteine at the time the invention was filed. In addition, the skilled artisan would recognize that Applicant was in possession of the sub-genus of genus amino acid derivative consisting of pharmaceutically acceptable salts of the amino acids. The skilled artisan would not conclude based on the breadth of the genus and lack of distinguishing features disclosed in the specification that pharmaceutically acceptable salts are representative of the full genus of amino acid derivatives. Therefore, compositions comprising the amino acids leucine, isoleucine, valine, lysine, threonine, histidine, methionine, phenylalanine, tryptophan, tyrosine and cysteine and pharmaceutically acceptable salts thereof meet the written description requirement of 35 U.S.C.

§ 112, first paragraph, but not the full genus of pharmaceutically acceptable amino acid derivatives.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 32-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 32-53 are drawn to compositions comprising the amino acids leucine, isoleucine, valine, lysine, threonine, histidine, methionine, phenylalanine, tryptophan, tyrosine and cysteine, or pharmaceutically acceptable derivatives of each of the aforementioned amino acids. The instant specification does not define the term derivative. The online medical dictionary defines derivative as a chemical substance derived from another substance either directly or by modification or partial substitution. Thus, the scope of claims 32-53 encompasses compositions comprising any chemical substance derived from leucine, isoleucine, valine, lysine, threonine, histidine, methionine, phenylalanine, tryptophan, tyrosine and cysteine directly, or any chemical substance consisting of leucine, isoleucine, valine, lysine, threonine, histidine, methionine, phenylalanine, tryptophan, tyrosine or cysteine that has been modified or partially substituted. The metes and bounds of this genus are not defined in the claim or the specification because neither define how much an amino acid may be modified, substituted or otherwise altered while still being considered a derivative of the amino acid.

7. Claims 39-42, 52 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 39-42, 52 and 53 each recite the limitation "other essential amino acids, or derivatives thereof, envisaged in the composition". The phrase " envisaged in the composition" renders the claim indefinite because it is unclear whether the other essential amino acids are part of the claimed invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. Claims 32, 35 and 43-48 are rejected under 35 U.S.C. 102(b) as being anticipated by Volpi *et al.* ("Exogenous Amino Acids Stimulate Net Muscle Protein Synthesis in the Elderly," *J. Clin. Invest.*, **1998**, *101*, 2000–2007).

Claim 32 is drawn to a method comprising administering to an elderly patient a therapeutically effective amount of a composition comprising, as active ingredients, the following: i) leucine, isoleucine and valine; ii) lysine; and iii) at least one of: a) threonine; or b) one or more selected from the group consisting of histidine, methionine, phenylalanine and tryptophan.

Volpi *et al.* teach a method of infusing amino acid compositions into elderly patients in order to stimulate net muscle protein synthesis (p. 2001 col 1). The amino acid infusion comprises [mg/ml and (μmol/l), respectively] alanine 20.7 (232.3), arginine 11.5 (66.0), glycine 10.3 (137.2), histidine 4.8 (30.9), isoleucine 6.0 (45.7), leucine 7.3 (55.6), lysine 5.8 (39.7), methionine 4 (26.8), phenylalanine 5.6 (33.9), proline 6.8 (59.1), serine 5.0 (47.6), threonine 4.2 (35.3), tryptophan 1.8 (8.8), tyrosine 0.4 (2.2), and valine 5.8 (49.5) (. The total amino acid infusion was 148.5 mg. (p. 2001 col 2). Volpi *et al.* teach that "amino acids alone can stimulate muscle protein anabolism in elderly individuals whose muscle mass was reduced, as compared to their younger counterparts. Increasing the amino acid delivery to the leg by the intravenous infusion of an amino acid mixture apparently increased net muscle protein synthesis by increasing inward amino acid transport." (p. 2004 col 2)

Volpi *et al.* teach all of the active method steps of claim 32. The patient population taught by Volpi *et al.* is elderly patients. The composition administered to the patients comprises i) leucine, isoleucine and valine; ii) lysine; iii) a) threonine and b) histidine, methionine, phenylalanine and tryptophan. The dose of the amino acid infusion administered to the elderly patients is therapeutically effective as evidenced by the fact that muscle protein anabolism was stimulated (p. 2004 col 2). The amino acids were active ingredients as evidenced by the teaching that the amino acids in the infusion are responsible for the increase muscle protein anabolism (p. 2004 col 2).

Volpi *et al.* do not explicitly teach that the method of administering the amino acid infusion in a therapeutically effective amount has the functional effect of maintaining intact, restoring and/or increasing the number of cellular mitochondria, a limitation recited in claim 32.

Because the method of Volpi *et al.* meets all of the active method steps of claim 32, this functional effect is inherently met. MPEP § 2112 states: "The discovery of a new use for an old structure based on unknown properties of the structure might be patentable to the discoverer as a process of using. *In re Hack*, 245 F.2d 246, 248, 114 USPQ 161, 163 (CCPA 1957). However, when the claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. *In re May*, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978) (Claims 1 and 6, directed to a method of effecting nonaddictive analgesia (pain reduction) in animals, were found to be anticipated by the applied prior art which disclosed the same compounds for effecting analgesia but which was silent as to addiction. The court upheld the rejection and stated that the applicants had merely found a new property of the compound and such a discovery did not constitute a new use." In the instant case, the use in claim 32, maintaining intact, restoring and/or increasing the number of cellular mitochondria, is directed to a result or property of the amino acid composition. The discovery that the amino acid composition has the effect of maintaining intact, restoring and/or increasing the number of cellular mitochondria does not constitute a new use of an old composition. This effect would result when the composition is administered to the same patient population regardless of whether or not the practitioner recognized the effect. Therefore, the claim is anticipated by Volpi *et al.*

With respect to claim 35, the amino acid infusion composition taught by Volpi *et al.* further comprises tyrosine (p. 2001 col 2).

Independent claim 43 is drawn to a method comprising administering to a subject a therapeutically effective amount of a composition comprising as active ingredient leucine,

isoleucine and valine. As stated above for claim 32, the method taught by Vopli *et al.* wherein an amino acid infusion comprising leucine, isoleucine and valine is administered to elderly patients in a therapeutically effective amount, meets the limitations of the claims. With respect to the limitation "for the treatment of apoptosis of mitochondrial origin," this is a functional effect or result of administering the composition that constitutes a discovery but not a new use of the composition.

With respect to claim 44, the composition further comprises lysine and threonine (p. 2001 col 2). With respect to claim 45, the composition further comprises lysine, threonine, histidine, methionine, phenylalanine and tryptophan (p. 2001 col 2). With respect to claim 46, the composition comprises tyrosine (p. 2001 col 2). With respect to claim 47, the composition further comprises threonine and lysine (p. 2001 col 2). With respect to claim 48, the composition further comprises lysine, threonine, histidine, methionine, phenylalanine and tryptophan (p. 2001 col 2).

10. Claims 43-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Ozeki *et al.* (US 5,036,052).

Independent claim 43 is drawn to a method comprising administering to a subject a therapeutically effective amount of a composition comprising as active ingredient leucine, isoleucine and valine.

Ozeki *et al.* teach several amino acid infusion compositions comprising **isoleucine**, **leucine**, lysine, methionine, phenylalanine, threonine, tryptophan, **valine**, alanine, arginine, aspartic acid, cysteine, glutamic acid, histidine, proline, serine, tyrosine and glycine (emphasis

added, Table 45). Ozeki *et al.* teach a method of making said compositions comprising mixing BCAA invented by Ozeki *et al.* with commercially available amino acid infusion solutions in various ratios to yield the compositions in Table 45. Ozeki *et al.* teach that "the BCAA composition of the present invention contains branched chain L-amino acids in a high concentration in a suitable ratio and is useful as a premixing preparation for preparing amino acid infusion solutions **for respective morbid conditions which are required to administer highly dense branched chain L-amino acids**. In other words, if a conventional amino acid infusion solution is mixed with a BCAA composition of the present invention in an appropriate ratio, then amino acid infusion solutions can readily be prepared which solutions are **suited for respective specific diseases**." (emphasis added, col 28, lines 8-21). Although Ozeki *et al.* do not explicitly teach a method of administering the amino acid infusion compositions of Table 45 to a subject in need thereof, the skilled artisan could readily envisage such a method from the teaching in col 28, lines 8-21. Therefore, a method of administering a composition comprising a therapeutically effective amount of the branched amino acids leucine, isoleucine and valine to a subject is anticipated by Ozeki *et al.* The limitation in claim 43 that administration of the composition treats "apoptosis of mitochondrial origin," is a functional effect or result that is inherent to the structure of the composition and to the method of administering it. Treating mitochondrial apoptosis using the amino acid composition does not constitute a new use of said composition but rather represents a discovery of a property or function that need not have been recognized in the prior art in order to anticipate the claim. See discussion of MPEP § 2112 above.

With respect to claims 44 and 47, the compositions further comprise threonine and lysine (Table 45). With respect to claims 45 and 48, the compositions further comprise threonine, lysine, histidine, methionine, phenylalanine and tryptophan (Table 45). With respect to claims 46 and 49, the composition further comprises threonine, lysine, histidine, methionine, phenylalanine, tryptophan, tyrosine and cysteine (Table 45).

With respect to claim 50, Table 45 of Ozeki *et al.* reports the amounts of amino acids in g/L. The amounts are converted to mol/L below.

			mol/L		
sample	1	2	3	4	5
Leu	0.1847	0.2344	0.1176	0.1473	0.1244
Ile	0.0901	0.1145	0.0542	0.0878	0.0802
Val	0.0949	0.1239	0.0530	0.1034	0.1282
Lys	0.0555	0.0418	0.0747	0.0945	0.0445
Thr	0.0353	0.0269	0.0479	0.0513	0.0571
His	0.0252	0.0187	0.0342	0.0000	0.0290
Met	0.0154	0.0114	0.0208	0.0899	0.0268
Phe	0.0370	0.0279	0.0497	0.0812	0.0388
Trp	0.0042	0.0031	0.0054	0.0147	0.0059
Tyr	0.0012	0.0009	0.0017	0.0000	0.0020
Cys	0.0054	0.0040	0.0073	0.0000	0.0000

The ratios of isoleucine, valine, threonine and lysine to leucine are as follows:

			molar ratio of amino acid /Leu			claimed
sample	1	2	3	4	5	
Ile	0.4876	0.4886	0.4610	0.5959	0.6442	0.2 to 0.7
Val	0.5136	0.5288	0.4508	0.7020	1.0304	0.2 to 0.7
Lys	0.3003	0.1783	0.6351	0.6416	0.3578	0.15 to 0.50
Thr	0.1911	0.1147	0.4075	0.3479	0.4592	0.15 to 0.6

Thus, sample 1 anticipates claim 50.

With respect to claim 51, the percentage of the sum in moles of leucine, isoleucine, valine, lysine and threonine that is the sum in moles of leucine, isoleucine, valine, lysine,

threonine, histidine, methionine, phenylalanine and tryptophan for the samples in Table 45 of Ozeki *et al.* is as follows:

1	2	3	4	5
17.7507	11.28178	31.6979	38.37402	23.14384

Samples 1, 2 and 5 fall within the claimed range of 2% to 25% and thus anticipate the claim.

11. Claims 32, 35, 38 and 43-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Dioguardi (U.S. Patent No. 6,218,420).

Dioguardi teaches a method for regulating nitrogen in a body, comprising administering thereto a composition comprising, as active ingredients: up to 75% of the BCAA leucine, isoleucine and valine; up to 50% of threonine and lysine; and up to 40% of one or more amino acids selected from the group consisting of cysteine, histidine, phenylalanine, methionine, tryptophan, and tyrosine; wherein threonine and lysine are present in larger quantities than the other essential amino acids of the composition, with the exception of the BCAA of the composition (claim 8). Dioguardi teach that in elderly people a reduction in digestive enzymes is observed which leads to a reduction in protein digestion and in turn, a reduction in amino acid absorption. In contrast, "free amino acids are instead absorbed without any contribution by the digestive system." (col 2 lines 54-60)

With respect to claims 43-49, administering to a body in claim 8 of Dioguardi satisfies the limitation administering to a subject. With respect to claims 32, 35 and 38, the patient population in claim 8 of Dioguardi is not limited to elderly. The skilled artisan could readily envisage administering the amino acid composition of claim 8 of Dioguardi to elderly patients, a

subgenus of the genus body, based on the teaching in col 2 lines 54-60 regarding amino acid absorption in the elderly.

With respect to the amino acid compositions recited in instant claims 32, 35, 38 and 43-49, claim 8 of Dioguardi is a generic claim that encompasses compositions comprising leucine, isoleucine and valine, threonine and lysine (satisfying instant claims 43, 44 and 47) and additional amino acids selected from the group consisting of 1) one or more of histidine, methionine, phenylalanine and tryptophan (satisfying instant claims 32 and 45); 2) one or more of histidine, methionine, phenylalanine and tryptophan and at least one of tyrosine and cysteine (satisfying instant claims 35 and 46); 3) histidine, methionine, phenylalanine and tryptophan (satisfying instant claim 48); and 4) histidine, methionine, phenylalanine, tryptophan, tyrosine and cysteine (satisfying instant claims 38 and 49). The skilled artisan could readily envisage these species given the limited number of compositions in the genus of claim 8 of Dioguardi.

The limitation in claim 32 regarding maintaining intact, restoring and/or increasing the number of cellular mitochondria and the limitation in claim 43 regarding the treatment of apoptosis of mitochondrial origin, are inherently met by Dioguardi which teaches all of the active method steps of the claims. These effects represent discoveries of properties or effects of the composition rather than a new use of an old product. See discussion of MPEP § 2112 above.

12. Claims 43-49 are rejected under 35 U.S.C. 102(e) as being anticipated by Conti *et al.* (U.S. 20040192756).

Conti *et al.* teach a method for the healing and/or mending of wounds and lesions in a body, comprising administering thereto a composition comprising proline, glycine and lysine, up

to 80 wt % on the total of all the administered amino acids, leucine, isoleucine and threonine, in an overall quantity of between 2 wt % and 60 wt % on the total of all the administered amino acids, valine, and one or more of the other essential amino acids phenylalanine, histidine, tryptophan and methionine (claim 35).

With respect to instant claim 43, Conti *et al.* teaches a method of administering a composition comprising leucine, isoleucine and valine to a subject (a body). With respect to claim 44, the composition further comprises threonine and lysine. With respect to claim 45, the composition further comprises one or more of the other essential amino acids phenylalanine, histidine, tryptophan and methionine. With respect to claim 46, the composition further comprises tyrosine. With respect to claim 47, the composition further comprises threonine and lysine. With respect to claim 48, the skilled artisan could readily envisage that the composition comprises phenylalanine, histidine, tryptophan and methionine based on the teaching that it comprise *one or more of* the other essential amino acids phenylalanine, histidine, tryptophan and methionine. With respect to claim 49, the composition further comprises tyrosine and cysteine (Conti *et al.* claim 38).

The limitation in claim 43 regarding the treatment of apoptosis of mitochondrial origin, is inherently met by Conti *et al.* which teaches all of the active method steps of the claims. This effect represents discovery of properties or effects of the composition rather than a new use of an old product. See discussion of MPEP § 2112 above.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37

CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

13. Claims 43-49 are rejected under 35 U.S.C. 102(e) as being anticipated by Conti *et al.* (U.S. 20040157903).

Conti *et al.* teach compositions comprising essential amino acids (leucine, isoleucine, valine, threonine, lysine, methionine, phenylalanine, histidine, tryphtophan) and some non essential amino acids (tyrosine and cyst(e)ine) (paragraph 0018). This composition satisfies the amino acid limitations of claims 43-49. Conti *et al.* teach administering the composition to subjects having type II diabetes (paragraph 0028).

The limitation in claim 43 regarding the treatment of apoptosis of mitochondrial origin, is inherently met by Conti *et al.* which teaches all of the active method steps of the claims. This effect represents discovery of properties or effects of the composition rather than a new use of an old product. See discussion of MPEP § 2112 above.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 33, 34, 36-42, 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Volpi *et al.* ("Exogenous Amino Acids Stimulate Net Muscle Protein Synthesis in the Elderly," *J. Clin. Invest.*, **1998**, *101*, 2000–2007), as applied to claims 32, 35 and 43-48 above, in view of Ozeki *et al.* (US 5,036,052), as applied to claims 43-51 above.

Volpi *et al.* teach a method of infusing amino acid compositions into elderly patients in order to stimulate net muscle protein synthesis (p. 2001 cols 1 and 2). The specifics of the composition are described above.

Volpi *et al.* do not teach that the composition comprises cysteine as recited in claims 37, 38 or that the composition comprises amino acids in the amounts recited in claims 33, 34, 36-39, 43 and 52.

Ozeki *et al.* teach several amino acid infusion compositions comprising isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine, alanine, arginine, aspartic acid, cysteine, glutamic acid, histidine, proline, serine, tyrosine and glycine (Table 45) suitable for administration to patients. The specifics of the composition are described above.

It would have been obvious to one of ordinary skill in the art to substitute the amino acid infusion compositions taught by Ozeki *et al.* for the amino acid infusion composition in the method taught by Volpi *et al.* The skilled artisan would have been motivated to do so given that

Ozeki *et al.* teach that the amino acid infusion compositions exhibit less degradation and discoloration than conventional amino acid infusion compositions without the additional of harmful or reactive stabilizers (col 2, lines 6-10). There would have been a reasonable expectation of success given that Ozeki *et al.* teach that compositions can be prepared specifically for various diseases (col 28, lines 8-21).

With respect to claims 37 and 38, the compositions taught by Ozeki *et al.* include cysteine.

With respect to claims 33, 34,36, 38-42, 52 and 53, it would have been obvious to optimize the amounts of amino acids in the infusion compositions through routine experimentation. MPEP § 2144.05 states: "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)" Furthermore, MPEP § 2144.05 states: "A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977)" In the instant case, the amount of amino acid in the composition is a result-effective variable because the amino acids are considered active ingredients (see Volpi *et al.*). Ozeki *et al.* discloses numerous samples throughout its disclosure (Tables 1-45) with different amounts and ratios of amino acids. The variation of amounts and ratios to achieve a desired

therapeutic benefit, such as stimulation of muscle in Volpi *et al.*, constitutes routine experimentation.

Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

16. Claims 33, 34, 36, 37, 39-42 and 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dioguardi (U.S. Patent No. 6,218,420), as applied to claims 32, 35, 38 and 43-49 above. The teaching of Dioguardi is described above. Dioguardi does not teach the concentrations, amounts and/or ratios recited in claims 33, 34, 36, 37, 39-42 and 50-53. It would have been obvious to optimize the concentrations, amounts and/or ratios of amino acids in the compositions of Dioguardi through routine optimization. See discussion of MPEP § 2144.05 above.

17. Claims 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Conti *et al.* (US 20040192756), as applied to claims 43-49 above. The teaching of Conti *et al.* is described above. Conti *et al.* do not teach the concentrations, amounts and/or ratios recited in claims 50-53. It would have been obvious to optimize the concentrations, amounts and/or ratios of amino acids in the compositions of Conti *et al.* through routine optimization. See discussion of MPEP § 2144.05 above.

18. Claims 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Conti *et al.* (U.S. 20040157903), as applied to claims 43-49 above. The teaching of Conti *et al.* is described above. Conti *et al.* do not teach the concentrations, amounts and/or ratios recited in claims 50-

53. It would have been obvious to optimize the concentrations, amounts and/or ratios of amino acids in the compositions of Conti *et al.* through routine optimization. See discussion of MPEP § 2144.05 above.

The applied references Conti *et al.* (U.S. 20040192756) and Conti *et al.* (U.S. 20040157903) have a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Double Patenting

19. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined

application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 43-53 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 9 of U.S. Patent No. 6,218,420. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claim 8 of U.S. Patent No. 6,218,420 recites a method for regulating nitrogen in a body, comprising administering thereto a composition comprising, as active ingredients: up to 75% of the BCAA leucine, isoleucine and valine; up to 50% of threonine and lysine; and up to 40% of one or more amino acids selected from the group consisting of cysteine, histidine, phenylalanine, methionine, tryptophan, and tyrosine; wherein threonine and lysine are present in larger quantities than the other essential amino acids of the composition, with the exception of the BCAA of the composition (claim 8).

With respect to claims 43-49, administering to a body in claim 8 of U.S. Patent No. 6,218,420 satisfies the limitation administering to a subject.

With respect to the amino acid compositions recited in instant claims 43-49, claim 8 of U.S. Patent No. 6,218,420 is a generic claim that encompasses compositions comprising leucine, isoleucine and valine, threonine and lysine (satisfying instant claims 43, 44 and 47) and

additional amino acids selected from the group consisting of 1) one or more of histidine, methionine, phenylalanine and tryptophan (satisfying instant claim 45); 2) one or more of histidine, methionine, phenylalanine and tryptophan and at least one of tyrosine and cysteine (satisfying instant claim 46); 3) histidine, methionine, phenylalanine and tryptophan (satisfying instant claim 48); and 4) histidine, methionine, phenylalanine, tryptophan, tyrosine and cysteine (satisfying instant claim 49). The skilled artisan could readily envisage these species given the limited number of compositions in the genus of claim 8 of U.S. Patent No. 6,218,420.

The limitation in claim 43 regarding the treatment of apoptosis of mitochondrial origin, are inherently met by claim 8 of U.S. Patent No. 6,218,420 which teaches all of the active method steps of the instant claims. These effects represent discoveries of properties or effects of the composition rather than a new use of an old product. See discussion of MPEP § 2112 above.

Claim 8 of U.S. Patent No. 6,218,420 does not teach the concentrations, amounts and/or ratios recited in claims 50-53. It would have been obvious to optimize the concentrations, amounts and/or ratios of amino acids in the compositions of Dioguardi through routine optimization. See discussion of MPEP § 2144.05 above.

21. Claims 43-53 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35-39 of copending application 10/486,141 (US 20040192756). Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 35 of copending application 10/486,141 recites a method for the healing and/or mending of wounds and lesions in a body, comprising administering thereto a composition

comprising leucine, isoleucine, valine, threonine and lysine, and one or more of the other essential amino acids phenylalanine, histidine, tryptophan and methionine, satisfying the active method steps of instant claims 43-45 and 47. Claim 37 states that the composition further comprises methionine or tyrosine and claim 38 states that the composition further comprises cysteine, satisfying the active method steps of instant claim 46. With respect to claim 48, the skilled artisan could readily envisage that the composition comprises phenylalanine, histidine, tryptophan and methionine based on the teaching that it comprise *one or more of* the other essential amino acids phenylalanine, histidine, tryptophan and methionine. With respect to claim 49, the composition further comprises tyrosine and cysteine.

The limitation in claim 43 regarding the treatment of apoptosis of mitochondrial origin, is inherently met by the claims of copending application 10/486,141 which teach all of the active method steps of the claims. This effect represents discovery of properties or effects of the composition rather than a new use of an old product. See discussion of MPEP § 2112 above.

Claim 35 of copending application 10/486,141 does not teach the concentrations, amounts and/or ratios recited in claims 50-53. It would have been obvious to optimize the concentrations, amounts and/or ratios of amino acids in the compositions of claim 35 of copending application 10/486,141 through routine optimization. See discussion of MPEP § 2144.05 above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. The provisional rejection on the ground of nonstatutory obviousness-type double patenting over application 10/480,774 is withdrawn because the case was abandoned on 07/18/2008.

23. Claims 43-53 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 33-54 of copending application 10/332,236. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 54 of copending application 10/332,236 recites a method of treating heart failure comprising administering to a subject a composition comprising the branched chain amino acids leucine, isoleucine and valine, at least one of methionine and phenylalanine, cysteine, at least one of threonine and lysine, and at least one selected in the group consisting of histidine, tryptophan, tyrosine, and cysteine, satisfying all of the active method steps of instant claims 43-46. With respect to claim 47, the skilled artisan could readily envisage the composition comprising threonine and lysine based on the language at least one of threonine or lysine. With respect to claims 48 and 49, the skilled artisan could likewise readily envisage the composition comprising histidine, methionine, phenylalanine, tryptophan, tyrosine and cysteine.

The limitation in claim 43 regarding the treatment of apoptosis of mitochondrial origin, is inherently met by the claims of copending application 10/332,236 which teach all of the active method steps of the claims. This effect represents discovery of properties or effects of the composition rather than a new use of an old product. See discussion of MPEP § 2112 above.

Claim 54 of copending application 10/322,236 does not teach the concentrations, amounts and/or ratios recited in claims 50-53. It would have been obvious to optimize the concentrations, amounts and/or ratios of amino acids in the compositions of claim 54 of copending application 10/322,236 through routine optimization. See discussion of MPEP § 2144.05 above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claims 43-53 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-35 of copending application 12/104,722. Although the conflicting claims are not identical, they are not patentably distinct from each other.

Claim 16 of copending application 12/104,722 recites a method for improving myocardial ventricular function in a patient suffering from diabetes, comprising administering to the patient a composition comprising branched chain amino acids leucine, isoleucine and valine, satisfying all of the active method steps of instant claim 43. Claim 19 states that the composition comprises at least one of threonine and lysine, and at one or more essential amino acids selected from the group consisting of methionine, phenylalanine, histidine and tryptophan, satisfying all active method steps of claims 44 and 45. The skilled artisan could readily envisage the composition recited in instant claim 46 based on conflicting claim 22 which states that the composition further comprises at least one of tyrosine and cyst(e)ine. Claim 18 states that the composition comprises both threonine and lysine, satisfying all of the active method steps of

instant claim 47. The skilled artisan could readily envisage the composition recited in instant claim 48 based on conflicting claim 21 which states that the composition comprises methionine, phenylalanine, histidine and tryptophan. The skilled artisan could readily envisage the composition recited in instant claim 49 based on conflicting claim 23 which states that the composition further comprises at least one of tyrosine and cyst(e)ine.

The limitation in claim 43 regarding the treatment of apoptosis of mitochondrial origin, is inherently met by the claims of copending application 12/104,722 which teach all of the active method steps of the claims. This effect represents discovery of properties or effects of the composition rather than a new use of an old product. See discussion of MPEP § 2112 above.

Claims 16-53 of copending application 12/104,722 do not teach the concentrations, amounts and/or ratios recited in claims 50-53. It would have been obvious to optimize the concentrations, amounts and/or ratios of amino acids in the compositions of claims 16-53 of copending application 12/104,722 through routine optimization. See discussion of MPEP § 2144.05 above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

25. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571)272-9044. The examiner can normally be reached on Monday-Thursday, 8:30 A.M. to 4:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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